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Review Article

Effectiveness of biomimetic nanohydroxyapatite on remineralisation of carious lesion: A systematic review

Snehal Babasaheb Shelke[1]*, **Manjusha M Warhadpande**[1], **Darshan M Dakshindas**[1], **Sulabha A Radke**[1]

[1]*Dept. of Conservative Dentistry, Government Dental College and Hospital, Nagpur, Maharashtra, India*

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ABSTRACT

Background: Dental caries is a prevalent infectious disease of the dental hard tissue. Simple non-invasive remineralization of dental caries may be sufficient to stop the progression of incipient carious lesions.
Materials and Methods: Research question was formulated based on the PICO strategy. A comprehensive electronic literature search was conducted, independently by two reviewers. Based on the specified inclusion and exclusion criteria, the selected articles were subjected to quality assessment and the risk of bias evaluation was done.
Objective: The objective of this study was to conduct a systematic review of the literature on effectiveness of nanohydroxyapatite on remineralization of caries in comparison with other conventional remineralizing agents.
Search strategy: A search was performed in electronic database (i.e. PubMed, Cochrane and google scholar) using search terms alone and in combination by means of PubMed search builder from January 2010 to January 2023.
Selection criteria: Studies were selected if they met the following criteria: randomized clinical trials comparing nanohydroxyapatite and other remineralizing agents for caries remineralization.
Results: Nanohydroxyapatite has comparable efficacy on remineralization of dental caries.
Conclusion: Biomimetic hydroxyapatite-containing, fluoride-free oral care products are effective in remineralization of dental caries, especially in children. Additional long-term studies employing standardized protocols are necessary to draw definitive findings about the effect of hydroxyapatite on remineralization of dental caries.
Key Message: Nano-hydroxyapatite is a biomimetic and have a remineralizing effect on early carious lesions.

1. Introduction

Dental caries is the most prevalent chronic disease worldwide.[1] Its dynamic pathogenesis involving mineral loss of dental hard tissues results in cycle of demineralization and remineralization phases. Modern dentistry aims to manage non-cavitated carious lesions non-invasively through remineralization in an effort to stop disease progression.[2] The use of fluorides has proved to be the most clinically effective caries preventing protocol based on large number of clinical trials however the use of fluoride is still a major concern.[3] Synthetic nanohydroxyapatite is a biocompatible material with similar chemical composition to the apatite crystals of human enamel, In recent years, several in vivo and in situ studies have focused on the clinical use of nanohydroxyapatite for remineralization of caries and

* *Corresponding author*.
E-mail address: snehalshelke3@gmail.com (S. B. Shelke).

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it has shown to fill enamel interprismatic spaces and remineralize the enamel. This review aims to critically appraise the literature related to the remineralizing potential of nanohydroxyapatite formulations on carious lesions. Also, it attempts to assess the quality of evidence and to explore the implications of these findings for clinical practice and future research planning.

2. Materials and Methods

2.1. Protocol and registration

The present systematic review was registered at the National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews (Registration number: CRD42022352064). This research protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines 2020. This review was conducted following the recommendations of the Cochrane Collaboration for systematic reviews.

2.2. Eligibility criteria

Table 1: The eligibility criteria for inclusion of the studies with regard to participants, intervention, comparator, and outcomes.

Inclusion criteria	Exclusion criteria
Participants (P): Healthy patients between 3 years to 50 years of age.	Case reports
Intervention (I): Nano-hydroxyapatite formulations	In vitro and animal studies
Comparator (C): No treatment, Placebo (negative control), saliva, ozone, other remineralizing agents (e.g. CPP-ACP; Fluorides)	Articles in other languages than English
Outcomes (O): Primary development of caries lesion (initiation and progression/regression), e.g., laser fluorescence, ICDAS score, enamel remineralization rate, directly through clinical examination, radiographic density change.	Studies in which full-text articles not retrieved
Study design (S):	Randomized Clinical trials

A systematic search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar and PubMed using MeSH words, text words and Boolean operators. The articles in the English language were considered. The period of publication considered was between 1-1-2010 to 1-1-2023.

2.3. Study selection

The titles and abstracts of all retrieved articles were screened by two independent reviewers, and irrelevant studies were excluded. Full texts of the eligible studies were obtained and thoroughly assessed by the two reviewers for inclusion. Disagreements were resolved through discussion. Concerned study authors were communicated for the unreported data or additional details.

2.4. Data collection process

Data collection was performed using a customized data extraction form including contents such as title of the study, author's name, duration of study, year of publication, study setting, study design, study population, types of intervention, types of the comparator, characteristics of participants (age and gender), inclusion and exclusion criteria, times of measurement, outcomes and concluding remarks.

2.5. Risk of bias in individual studies

To determine the validity of the included RCTs, a tool developed by the Cochrane Collaboration was used to assess the risk of bias in clinical trials quality of included studies.

2.6. Synthesis of results

Findings from the studies were summarised in a narrative form, with particular attention paid to participant characteristics, intervention details (formulations used, amount of nanohydroxyapatite used), and outcome evaluation. Summaries of intervention effects for each study were provided by calculating risk ratio (for dichotomous outcomes) or standardized mean difference (for continuous outcomes). Heterogeneity of the previously mentioned characteristics was assessed using Chi-square test.

2.7. Literature search and study selection

Figure 1 shows the study search process according to the PRISMA guidelines. Electronic screening of PubMed and Google scholar identified 55 articles. From the 55 articles removing the duplicates, 29 full texts articles were screened on the basis of title and abstract.10 were excluded as the measure of outcome was not relevant to this study. A total of 19 articles were assessed for eligibility, among them, 11 articles were excluded due to following reasons:

1. Four studies were in situ studies.
2. One study was quasi experimental study.
3. The patients did not have early carious lesion in three studies.
4. In three studies intervention did not include hydroxyapatite.

Total 8 articles were included for qualitative analysis.

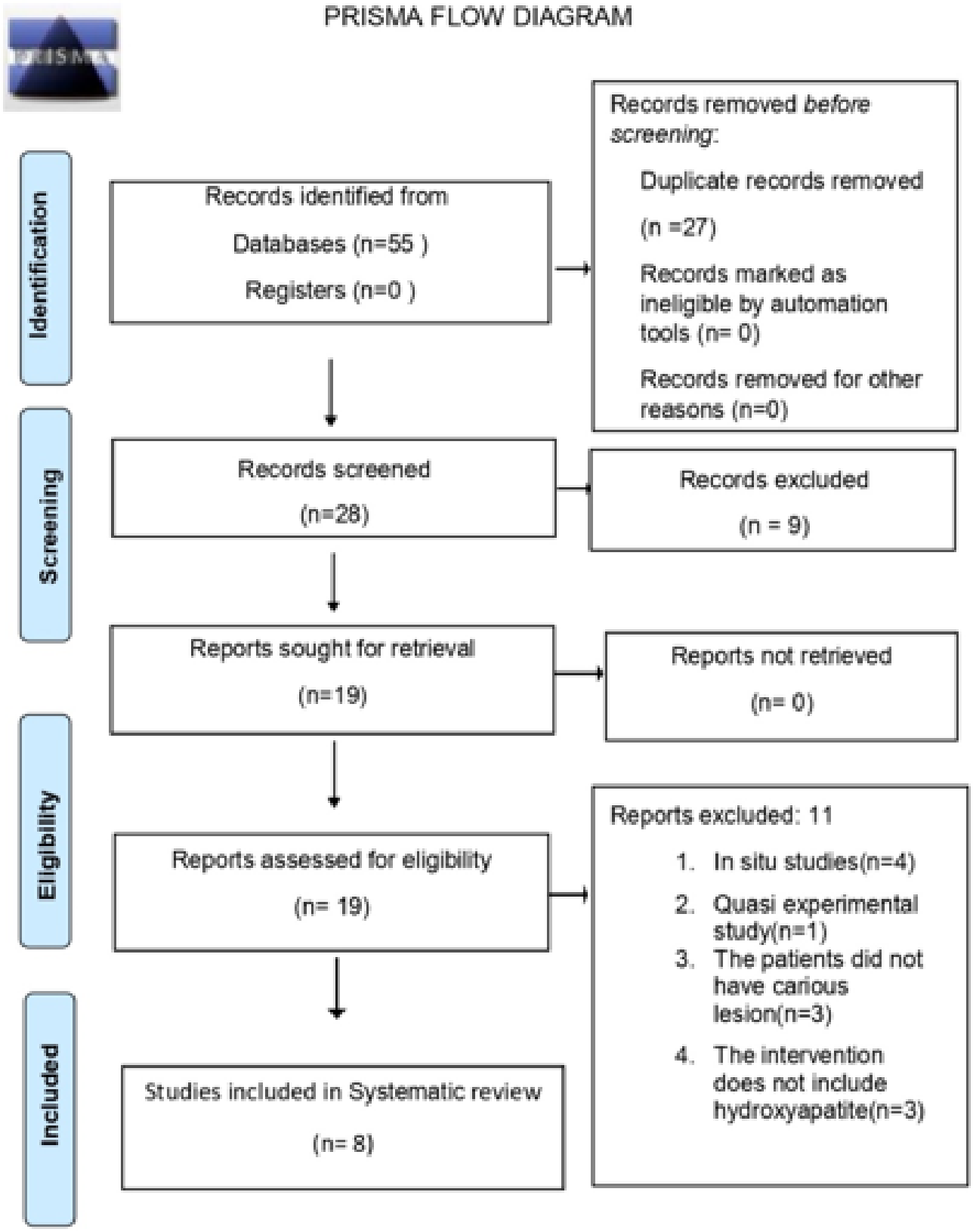

Figure 1: Prisma flow diagram.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71For more information, visit:http://www.prisma-statement.org/

Table 2: The general characteristics of included studies.

S.No	Author of the study	Year of study	Study design	Age of Patient	Study Sample	Hydroxyapatite Product	Control Group	Evaluation Method	Follow Up	Outcome
1.	Schlagenhauf et al.[4]	2019	Randomized clinical trial	12-25 years	150	Karex (10% HAP)	Toothpaste containing 1400 ppm fluoride (amine fluoride + stannous fluoride)	New caries measured using ICDAS	6 months	54.7% % increase in ICDAS score in HAP group 60.9 % increase in ICDAS score in FLUORIDE group
2.	Alhamed et al.[5]	2019	Randomized clinical trial	20-40 years	90	Nano-Hydroxyapatite gel – CTx4 Gel 1100 (CariFree, Canada	1.Fluoride varnish 25 ml (5% NaF) 2.TCP paste (ClinproTM)	Diagnodent	5 weeks	Nanohydroxyapatite was better than control group for remineralization.
3.	Badiee et al.[6]	2020	Randomized clinical caries trial	10 years to 35 years	50	7% HAP toothpaste formulated for the trial	Fluoride toothpaste	DIAGNOdent,photographic pixel changes	6 months	HAP has better remineralization than fluoride
4.	Grocholewicz et al.[7]	2020	Randomized clinical caries trial	20 to 30 years	92	ApaCare Repair (10% HAP gel)	1.Ozone (OzonyTron application) 2. HAP gel + ozone	Interproximal digital radiography of incipient caries remineralization	2 years	Caries reversal rate in HAP group 18.0%. In ozone group it was 38.0%, and in combination of both it was 45.4%
5.	Polykova et al.[8]	2020	Randomized clinical trial	20–25 years	60	hydroxyapatite 6%	Brushite formation toothpaste	Enamel remineralization rate	1 month	No statistically significant difference was found in the Enamel remineralization rate between two groups.
6.	Paszynska et al.[9]	2021	Randomized clinical trial	3 -7 years	177	Kinder Karex (10% HAP)	Elmex Kinder Zahnpasta (500 ppm fluoride)	New caries measured using ICDAS.	1 year.	Increase in ICDAS ≥ 1 in HAP group was 72.7% In FLUORIDE group it was 74.2 %
7.	Butera et al.[10]	2022	Randomized clinical trial	18–40 years	40	Hydroxyapatite (18% w/v)	Sodium Fluoride (1450 ppm F^-,Sodium monofluorophosphate (1000 ppm F^-)	Basic Erosive Wear Examination (BEWE)	6 months	BEWE scores did not significantly vary during the follow up neither in the trial nor in the control group.
8.	Cagetti et al.[11]	2022	Randomized controlled trial	4–5 and 6–7 years	610	HAF (1000 ppm F-) for 4-5 years children HAF (1450 ppm F-) for 6-7 years children	(1000 ppm F-) for 4-5 years children (F ± 1450 ppm F-) for 6-7 years children	New caries measured using ICDAS	2 years	39% reduction in risk ratio for caries as compared to control group.

ICDAS: International Caries Detection and Assessment System, HAP: Hydroxyapatite, F: Fluoride.

2.8. Quality of included studies

The results of the quality assessment were evaluated according to Cochrane Tool. Based on Cochrane's quality assessment tool for randomized control trial, included studies showed good quality assessment. Selection and detection bias was found in most of the studies.

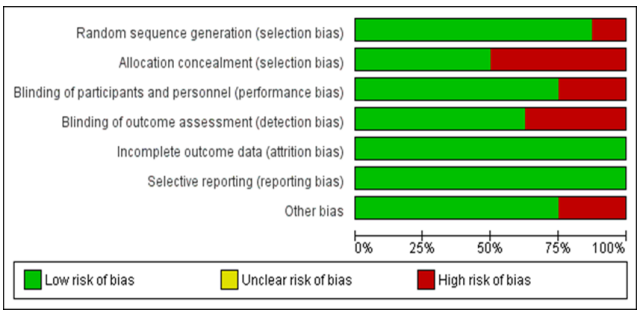

Figure 2: Overall risk of bias assessment of included randomized controlled studies.

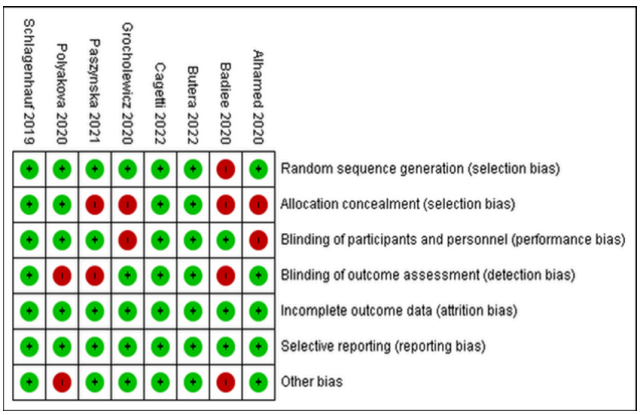

Figure 3: Risk of bias assessment of included randomized controlled studies

3. Discussion

The primary purpose of this systematic review was to summarize the evidence from multiple clinical trials that have compared the effectiveness of biomimetic nanohydroxyapatite for the remineralization of carious lesions.

3.1. The level of evidence

Risk of bias due to confounding factors, selection of participants in the study, classification of interventions, deviations from intended intervention, measurement of outcomes, and selection of the reported results were low in the RCT Studies.

3.2. Heterogeneity

3.2.1. Subject differences

There was a wide range of age for the participants included in the studies from 3 years[8] to 40 years.[5,10] Cagetti et al. compered the remineralization Efficacy of HAF toothpastes in primary and permanent dentitions and concluded that the use of fluoridated toothpaste had a preventive effect in the younger group only however the hydroxyapatite toothpaste had efficacy in both younger and older group.[11] Daruich et al.reported that Dental caries remineralization depends on the patient's health, maintenance of oral hygiene, and the extent and severity of the lesion and also on the structural and functional features of its surface layer.[12] The influence of age and gender on the remineralization of carious lesion was non-significant.[6]

3.2.2. Intervention used

Remineralization refers to the treatment for an active initial carious lesion, by stopping the progression of the lesion to cavitated stages.[13] HAP particles penetrate enamel defects on the surface and below the surface to adhere to existing enamel structure. The ions produced as a result of biofilm acid dissolution of some HAP particles also contribute to the remineralization of enamel as it repairs after the acid attack is over. HAP particles have been shown to bind to biofilm bacteria, inhibit their activity, and act as an abrasive to prevent biofilm accumulation to fill enamel interprismatic spaces, restoring the mineral loss.[13]

Different nanohydroxyapatite formulations were used in different studies with the concentration ranging from 6% to 18%.with the increased rate and amount of nHAP precipitation there was an increase in the deposition of calcium and phosphate ions,[14] as well as the surface hardness of the demineralized enamel.[15] Although 15% nHAP demonstrated efficient remineralization, this concentration was too high for practical usage as it generate some level of aggregation.[14] Moreover, 10% nHAP showed similar results as compared with 15% nHAP. The rate of remineralization was the fastest during the first 6 days of pH cycling, and then gradually reduced and stabilized beyond this point.[16] Nanohydroxyapatite can be used as a nontoxic alternative for the remineralization of carious lesion.

3.2.3. Remineralizing agents

Fluoride at a concentration of 1000–1450 parts per million has been utilized as a preventive and remineralization agent due to its ability to promote the development of Fluorapatite.[17] Calcium phosphate-based treatment has also been identified as a possible alternative remineralizing agent with anti-caries effects. Casein phosphopeptide-amorphous calcium phosphate is one such agent (CPP-ACP) and it has been shown to suppress demineralization by releasing calcium and phosphate ions in low pH conditions, such as those present in carious lesions; however, there are only

a few studies that support its use.[18] The remineralizing potential of nHAP is comparable with that of fluoride, when compared with CPP-ACP formulations or with other dentifrices nHAP performed better.[4]

3.2.4. Assessment of remineralization

The remineralizing effect on the carious lesion in most of the studies is done using the direct visual examination, DMFT index, ICDAS score, DIAGNOdent, X ray analysis. DIAGNOdent is a laser device that measures fluorescence and improves the diagnostic accuracy of detection of non-cavitated carious lesions. Visual examination may lead to bias due to interexaminer differences. The ICDAS criteria was developed to integrate several new criteria systems into one standard system for caries detection and assessment to use in dental education, clinical practice, research, and epidemiology.[19]

DIAGNOdent was used in two studies for the assessment of remineralization.[5,6] ICDAS criteria and direct visual examination was done in five studies.[6–9,11] The relief from the clinical signs and symptoms such as degree or characteristic of hypersensitivity do not precisely reflect the remineralization potential however, nHAP is effective in hypersensitivity management. Among all studies included in review, two clinical studies[5,6] reported that the nHAP performed significantly better as compared to fluoride. All other included clinical trials reported with comparable remineralization with nHAP when combined with other methods of remineralization.

4. Limitations

Caries evaluation was not consistent across the studies and analysis of heterogeneity was not performed. Better studies including standardized protocols and caries assessment should be done to get to definite conclusion regarding remineralization potential of nanohydroxyapatite

5. Conclusion

Biomimetic hydroxyapatite-containing, fluoride-free oral care products are effective in remineralization of dental caries, especially in children. Additional long-term studies employing standardized protocols are necessary to draw definitive findings about the effect of hydroxyapatite on remineralization of dental caries.

6. Source of Funding

Self-supported.

7. Conflicts of Interest

There are no conflicts of interest.

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Author biography

Snehal Babasaheb Shelke, Post Graduate Student https://orcid.org/0000-0003-3270-4603

Manjusha M Warhadpande, Post Graduate Student https://orcid.org/0000-0002-1534-5015

Darshan M Dakshindas, Associate Professor https://orcid.org/0000-0001-9142-1078

Sulabha A Radke, Associate Professor https://orcid.org/0000-0001-6081-2738

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